# Stereoselective Synthesis of Highly Substituted Enamides by an Oxidative Heck Reaction\*\*

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#### Dedicated to Professor Eun Lee

The Heck arylation has proven to be among the most versatile reactions for C-C bond formation owing to its excellent chemoselectivity, wide functional group tolerability, and simplicity.<sup>[1]</sup> The palladium(0)-mediated catalytic process allows for facile cross-coupling of alkenes with various aryl and heteroaryl halides/pseudohalides. The oxidative Heck reaction has drawn significant attention where arylpalladium(II) species are generated by transmetalation with organometallic counterparts followed by undergoing insertion with alkenes.<sup>[2]</sup> Among the organometallic coupling partners, organoboronic acids have been extensively explored in various transition-metal-mediated reactions owing to their stability, wide availability, and low toxicity. Since the first demonstration of catalytic, oxidative Heck cross-coupling using arylboronic acids by Cho and Uemura,<sup>[2b]</sup> significant progress has been made. Despite the recent advances in the field, the limited substrate scope including necessitating steric/electronic bias prompt further improvements. For example, a literature survey shows that examples of Heck cross-coupling with electron-rich alkenes such as enamides are limited to those with simple unsubstituted vinyl groups.<sup>[3]</sup>

β-Amidoacrylate moiety represents an important motif that has been widely utilized as synthetic intermediates in the total synthesis of natural products<sup>[4]</sup> as well as preparation of heterocycles<sup>[5]</sup> and β-amino acids through asymmetric hydrogenation.<sup>[6]</sup> These compounds are typically prepared by condensation of β-ketoesters with amides,<sup>[7]</sup> and acylation of β-aminoacrylates.<sup>[8]</sup> Also, transition-metal-mediated reactions have been reported including oxidative amidation of acrylates<sup>[9]</sup> and addition of amides to terminal alkynes,<sup>[10]</sup> which typically provide disubstituted enamides. However, the limitations of these reactions include intolerance for sterically demanding substrates. Thus, finding an efficient synthesis of sterically hindered enamides, such as trisubstituted enamides bearing tertiary amides, remains a challenge.

 [\*] Y. Liu, D. Li, Prof. Dr. C.-M. Park Division of Chemistry and Biological Chemistry School of Physical and Mathematical Sciences Nanyang Technological University, Singapore 637371 (Singapore) Fax: (+65) 6513-2748 E-mail: cmpark@ntu.edu.sg In our efforts to develop a synthetic route for the synthesis of structurally diverse  $\beta$ -amino acids, we envisioned that Heck cross-coupling of  $\beta$ -amidoacrylates would provide  $\beta$ -aryl  $\beta$ -amidoacrylates which could be subsequently converted into  $\beta$ -amino acid derivatives by asymmetric hydrogenation [Eq. (1)]. Thus, we began by surveying Heck conditions



reported in the literature employing **1a** as a substrate (see Table 1 for structure). To our surprise, none of the conditions that we have attempted afforded the Heck products presumably owing to steric and electronic deactivation (see the Supporting Information). Tuning the balance between reactivity and stability of reactants in catalytic reactions is deemed to be among the key factors. The outcomes of the attempted reactions led us to seek the reaction parameters where aryl metal species possess sufficient stability under the reaction conditions, yet activation of which provides the reactivity to participate in the catalytic cycle. Herein, we describe our efforts to develop oxidative Heck conditions that allow for the stereoselective synthesis of  $\beta$ -substituted  $\beta$ -amidoacrylates and their derivatives in high yields.

We commenced with a brief screening of solvents employing **1a** and potassium phenyltrifluoroborate<sup>[11]</sup> as the coupling partner in the presence of Pd(OAc)<sub>2</sub> (10 mol%), Cu(OAc)<sub>2</sub> (3 equiv), and K<sub>2</sub>CO<sub>3</sub> (2 equiv): we quickly identified 20% AcOH in tert-BuOH as an optimal solvent (see the Supporting Information). Interestingly, while the use of either 1,4dioxane or tert-BuOH afforded moderate yields when a stoichiometric amount of Cu(OAc)2 was employed (50% and 54%, respectively), they were found to be detrimental to the reaction during our screening of oxidants where a catalytic amount of Cu(OAc)<sub>2</sub> under 1 atm oxygen was used (1,4dioxane; 18% and tert-BuOH; 0%). On the other hand, pure AcOH as a solvent also resulted in a poor yield (23%).<sup>[12]</sup> The structure of 3aa was unequivocally determined by X-ray crystallographic analysis.<sup>[13]</sup> In the screening of bases, the effect of counter cations clearly stood out with larger cations such as potassium and cesium preferred over sodium (Table 1, entry 1 vs. 2-4).

With these results in hand, we turned our attention to the screening of oxidants. Although common oxidants such as

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Table 1: Optimization of oxidative Heck cross-coupling reaction.[a-d]



[a] ArBF<sub>3</sub>K and ArB(Pin); 2 equiv used, and ArB(OH)<sub>2</sub>; 1.5 equiv used. [b] entries 1–9; 3 equiv of oxidant, 80 °C. [c] entries 10–18; 20 mol% of Cu(OAc)<sub>2</sub>, 1 atm of O<sub>2</sub>, 80 °C. [d] entries 19–24; 5 mol% of Cu(OAc)<sub>2</sub>, 1 atm of O<sub>2</sub>, 90 °C, 24 h. [e] Yield determined by GC methods. [f] 30 mol% of ligand. [g] 15 mol% of ligand. [h] 3 equiv of additive. [j] 8 equiv of additive. [j] Yield determined by <sup>1</sup>H NMR spectroscopy. Pin = pinacolate, dmphen = 2,9-dimethylphenanthroline, dppf=1,1'-bis(diphenylphosphanyl)ferrocene, BINAP=*rac*-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, bpPCy<sub>2</sub>=2-(dicyclohexylphosphino)biphenyl, BQ = benzoquinone.

Ag<sub>2</sub>O and AgF showed comparable results to  $Cu(OAc)_2$ , it is of note that the use of a catalytic amount of  $Cu(OAc)_2$ (20 mol%) in conjunction with oxygen (1 atm) as a terminal oxidant significantly improved the product yield (68%, entry 10). Careful analysis of the two reactions employing stoichiometric and catalytic amounts of  $Cu(OAc)_2$  revealed that a large amount of  $Cu(OAc)_2$  turns out to be detrimental, and promoted rapid protodeborylation (entry 3). However, the reaction conditions employing a catalytic amount of  $Cu(OAc)_2$  also gave a poor result when electron-rich 4methoxyphenyltrifluoroborate was used as a coupling partner. This reaction produced a substantial amount of the protodeborylation product (entry 11).

Thus, with the anticipation that the use of different forms of arylboron derivatives would lead to an improvement by altering factors such as the stability of arylboron compounds and rate of reaction of transient intermediates in the catalytic cycle, we examined arylboronic acids and arylboronates.<sup>[14]</sup> Although phenylboronic acid gave a poor result (23%), addition of KHF<sub>2</sub> improved the coupling yield (52%; entry 12 vs. 13). Encouraged by this result, we initiated the screening of ligands. The use of nitrogen-based ligands such as dmphen appeared to inhibit the catalytic cycle, and afforded the product in 26% yield (entry 14). Among the phosphine-based ligands screened, bpPCy<sub>2</sub> (2-(dicyclohexylphosphino)biphenyl)<sup>[15]</sup> afforded the Heck product in 64% yield (entry 17). While considering the possibility of the corresponding phosphine oxide bpP(O)Cy<sub>2</sub> serving as the active ligand under the oxidative conditions, we found that it failed to give any product (see the Supporting Information). Other phosphine ligands such as binap and dppf showed either inhibition or only marginal improvement (an extensive list of ligand screening can be found in the Supporting Information). However, 4-methoxyphenylbororic acid continued to give a poor yield under the reaction conditions (31%, entry 18).

Noting that the electron-rich aryl trifluoroborate and arylboronic acid rapidly undergo protodeborylation under the reaction conditions, we attempted the use of arylboronate anticipating an improved life span of arylboron species under the reaction conditions. Indeed, the use of pinacol 4-methoxyphenylboronate significantly improved the yield of the coupling product (75%, entry 24) in contrast to the corresponding trifluoroborate and boronic acids (38% and 31%, respectively). Consistently, the use of pinacol phenylboronate also resulted in an improved yield (74%, entry 22). A control experiment lacking the ligand underscores its pivotal role in the reaction (42%, entry 23). Screening of fluoride sources identified KHF<sub>2</sub> as an optimal additive (entries 19–22).

Having identified the optimized reaction conditions, we began to survey the substrate scope of the reaction. Substrates used to investigate the scope of the reaction were E isomers except for 1d. Notably, regardless of the geometry of alkenes in substrates, the coupling reactions result in Z isomers. Examination of the electronic influence of aryl groups revealed that those with both electron-donating and -withdrawing groups are well-tolerated and gave products in good to excellent yields (Table 2, 3ab-ae). However, the reactions of arylboronates with ortho-substituents were sluggish. To gain access to structurally diverse enamides, we examined substitution of pyrrolidinone with a variety of amide groups including secondary, tertiary, cyclic, acyclic, and aromatic amides. As shown in Table 2, the method allows for the synthesis of diverse enamides in high yields. In addition, those containing oxazolidinones in place of amides also afforded products in high yields (Table 2, 3 fa, 3ga, 3ia, 3ja). More-



[a] 2 equiv of pinacol arylboronates. [b] Yield of isolated products. [c] Reaction time was 4 days. [d] Z isomer used as the substrate. [e] 11% of  $\beta_i\beta_i$ -diphenyl product **3 ja**' was also isolated.

over, despite the steric hindrance, the reaction of substrate **1g** with Evans chiral oxazolidinone gave the product in 59% yield. This outcome shows potential in an application of asymmetric reduction based on a chiral auxiliary. We were also gratified to find that the reaction with highly deactivated alkene **1h** also proceeded smoothly to give product **3ha** in 59% yield. Next, we examined functional group tolerability of substrates with **1i** bearing an amide group in place of ester groups. The reaction also proceeded smoothly and afforded **3ia** in an excellent yield. Likewise, **1j** with an aryl group gave the coupling product in a high yield. This result indicates that an electron-withdrawing group is not a requisite, although the regioselectivity of  $\alpha/\beta$  decreases for those lacking an electron-withdrawing group (6.8:1 favoring  $\alpha$  substitution in this case).

To probe if the amide carbonyl groups serve as directing groups in the reaction, we attempted a reaction by employing a substrate lacking a carbonyl group. However, the instability of the substrate in the acidic medium led to hydrolysis of the



substrate. While directing groups are routinely employed to facilitate C–H bond activation,<sup>[16]</sup> their presence is not required in Heck reaction. Nevertheless, we cannot rule out the possibility in more challenging substrates.

Next, we turned our attention to the transformation of enamides into  $\beta$ -amino acid derivatives. Subjection of enamide **3 aa** to the asymmetric hydrogenation conditions employing the catalyst generated from [Rh(cod)<sub>2</sub>]BF<sub>4</sub> and (*R*)-Binaphane<sup>[17]</sup> smoothly produced compound **4** in 99% yield and 93% *ee* (see the Supporting Information).

In summary, we have developed efficient oxidative Heck cross-coupling conditions that allow for the synthesis of highly substituted enamides that are important synthetic intermediates with a broad utility in various applications. It is notable that modulation of stability and reactivity of arylboron species was found to be the key for the reaction such that the increased life span of arylboron species leads to a decreased background reaction and yet sufficiently reactive to participate in the catalytic cycle upon activation. This reasoning allowed us to identify the described reaction parameters.

### **Experimental Section**

1a (42 mg, 0.25 mmol), 4-methoxyphenylboronic acid pinacol ester **2b** (117 mg, 0.50 mmol), Pd(OAc)<sub>2</sub> (5.6 mg, 10 mol%), Cu(OAc)<sub>2</sub> (2.3 mg, 5 mol%), 2-(dicyclohexylphosphino)biphenyl (26 mg, 30 mol%), K<sub>2</sub>CO<sub>3</sub> (69 mg, 2 equiv), and KHF<sub>2</sub> (78 mg, 4 equiv). tert-BuOH-AcOH (4:1, 2.5 mL) were added to a flask that was subsequently evacuated and back-filled with O2 three times before being heated to 90 °C under O2 (1 atm). The progress of the reaction was monitored by TLC and GC analysis. Upon completion, the reaction mixture was cooled to RT, diluted with ethyl acetate, and filtered through a small pad of Celite. The filtrate was concentrated in vacuo, and the crude material was purified by flash chromatography on silica gel (eluent: 40% hexanes/ethyl acetate) to afford the product 3ab (50 mg, 72%, white solid, mp 88-89°C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.41$  (d, J = 8.8 Hz, 2 H), 6.91 (d, J = 8.8 Hz, 2H), 6.21 (s, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.56 (t, J=7.0 Hz, 2H), 2.60 (t, J = 8.0 Hz, 2 H), 2.23–2.15 ppm (m, 2 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 175.44$ , 165.13, 161.68, 148.32, 128.56, 126.94, 114.38, 112.38, 55.42, 51.46, 49.26, 31.72, 19.21; HRMS (ESI): m/z calcd for C<sub>15</sub>H<sub>18</sub>NO<sub>4</sub> [*M*+H]<sup>+</sup>: 276.1236; found: 276.1239.

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